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Health and Environmental Effects Profile for Aminophenols

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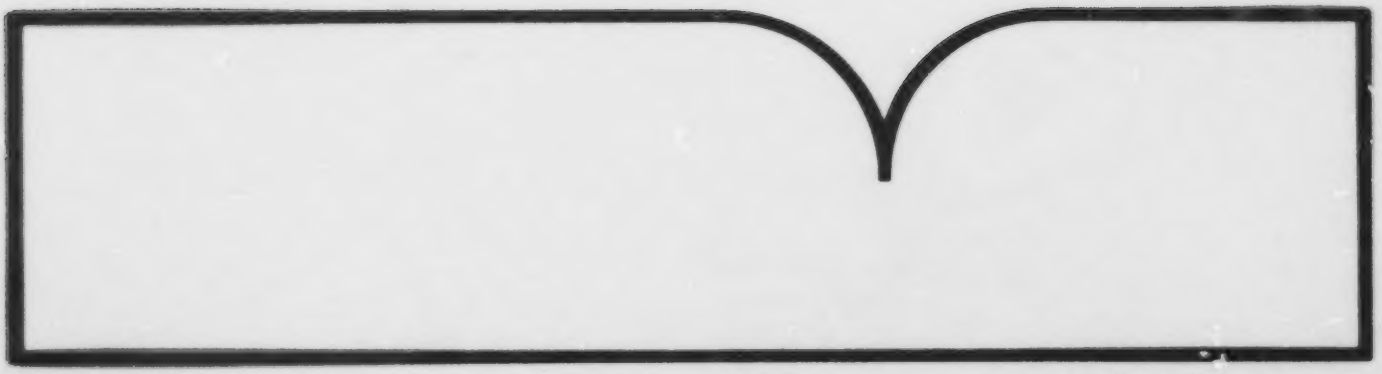

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16. ABSTRACT

The Health and Environmental Effects Profile for aminophenols was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Aminophenols has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for aminophenols is 4.55 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for aminophenols is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR AMINOPHENOLS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	1
1.4.	USE DATA	7
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	9
2.1.	WATER	9
2.2.	AIR	14
2.3.	SOIL	14
2.4.	SUMMARY	16
3.	EXPOSURE	18
3.1.	WATER	18
3.2.	FOOD	18
3.3.	INHALATION	18
3.4.	DERMAL	18
4.	PHARMACOKINETICS	19
4.1.	ABSORPTION	19
4.2.	DISTRIBUTION	20
4.3.	METABOLISM	20
4.4.	EXCRETION	22
5.	EFFECTS	23
5.1.	CARCINOGENICITY	23
5.2.	MUTAGENICITY	23
5.3.	TERATOGENICITY	32
5.4.	OTHER REPRODUCTIVE EFFECTS	36
5.5.	CHRONIC TOXICITY	37
5.6.	OTHER RELEVANT INFORMATION	38
6.	AQUATIC TOXICITY	49
6.1.	ACUTE TOXICITY	49
6.2.	CHRONIC EFFECTS	49
6.3.	PLANT EFFECTS	49
6.4.	RESIDUE	49
6.5.	OTHER RELEVANT INFORMATION	49
7.	EXISTING GUIDELINES AND STANDARDS	51
7.1.	HUMAN	51
7.2.	AQUATIC	51

Page

8. RISK ASSESSMENT 52

9. REPORTABLE QUANTITIES 56

9.1. REPORTABLE QUANTITY RANKING (RQ) BASED ON CHRONIC TOXICITY 56

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY. 62

10. REFERENCES. 63

APPENDIX: LITERATURE SEARCHED. 85

LIST OF TABLES

No.	Title	Page
1-1	Synonyms, CAS Numbers, Molecular Weights, Empirical Formulas and Structures of Aminophenols.	2
1-2	Physical Properties of Selected Aminophenols	3
1-3	Production Data for Aminophenols	4
2-1	Biodegradability Tests and Results for m-Aminophenol	12
4-1	Percentage of Administered Dose Recovered from the 24-Hour Urine of Rabbits Treated Orally with Aminophenols.	21
5-1	Animal...Agent: o-Aminophenol.	24
5-2	Mutagenicity of p-Aminophenol.	25
5-3	Mutagenicity of m-Aminophenol.	28
5-4	Mutagenicity of o-Aminophenol.	30
5-5	Teratogenicity of o-, m-, and p-Aminophenol in Syrian Golden Hamsters.	33
5-6	Types and Incidence of Malformations in the Syrian Golden Hamster Treated with o-, m-, and p-Aminophenol	35
5-7	Lethality of the Aminophenols.	39
9-1	Composite Scores for Oral Exposure to m-Aminophenol in the Rat	58
9-2	m-Aminophenol: Minimum Effective Dose (MED) and Reportable Quantity (RQ)	59
9-3	o-Aminophenol, o-Aminophenol Sulfate, o-Aminophenol Hydrochloride: Minimum Effective Dose (MED) and Reportable Quantity (RQ)	60
9-4	p-Aminophenol, p-Aminophenol Sulfate, p-Aminophenol Hydrochloride: Minimum Effective Dose (MED) and Reportable Quantity (RQ)	61

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BODT	Biochemical oxygen demand, theoretical
BUN	Blood urea nitrogen
bw	Body weight
CAS	Chemical Abstracts Service
COD	Chemical oxygen demand
CS	Composite score
DMSO	Dimethyl sulfoxide
DOC	Dissolved organic carbon
DNA	Deoxyribonucleic acid
K_m	Michaelis-Menten constant and is equal to 1/2 V_{max}
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LT_{50}	Median lethal time
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

LIST OF ABBREVIATIONS (cont.)

SCE	Sister chromatid exchange
UV	Ultraviolet
V_{max}	Maximum velocity of a reaction under the conditions in which the Michaelis-Menten equation holds true
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The CAS Registry numbers, molecular weights, empirical formulas, structures and common synonyms of the aminophenols and the aminophenol sulfates and hydrochlorides are presented in Table 1-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The physical properties of the aminophenols and salts are listed in Table 1-2.

o-Aminophenol and p-aminophenol as well as monosubstituted phenols are unstable in air and light and are rapidly oxidized to brown or black substances (Farris, 1978; Windholz, 1976). However, the sulfate and hydrochloride salts are more stable than the unsubstituted or the monosubstituted aminophenols (Farris, 1978). Atmospheric oxidation of o-aminophenols yields phenoxazines (Farris, 1978). In contrast to the other isomers, m-aminophenol is fairly stable in air (Werner, 1947).

1.3. PRODUCTION DATA

SRI (1984) lists the following manufacturers of aminophenols:

<u>o-aminophenol</u>	
Ciba-Geigy (Toms River Chemical) Corp.	Toms River, NJ
Mobay Chemical	Bushy Park, SC
<u>p-aminophenol</u>	
Avon Products (Mallinckrodt)	Raleigh, NC

USITC (1984a) lists Schenectady Chemical and Mallinckrodt as p-aminophenol manufacturers during 1983; however, no other aminophenols being considered are listed. Production data available from the U.S. EPA's TSCA Production File for 1977 are listed in Table 1-3; these data include manufacturers,

TABLE 1-1

Synonyms, CAS Numbers, Molecular Weights, Empirical Formulas and Structures of Aminophenols

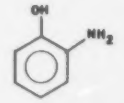
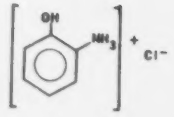
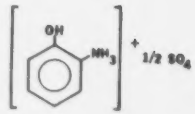
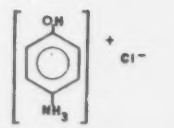
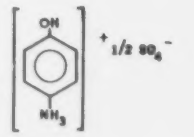
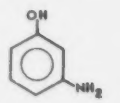
Aminophenol/Synonyms	CAS Number	Molecular Weight	Empirical Formula	Structure
o-Aminophenol 2-aminophenol 1-amino-2-hydroxybenzene 2-hydroxy aniline o-hydroxyphenylamine C.I. 76520	95-55-6	109.13	C_6H_7NO	
o-Aminophenol hydrochloride 2-aminophenol hydrochloride	51-19-4	145.52	$C_6H_7NO \cdot HCl$	
o-Aminophenol sulfate 2-aminophenol sulfate o-aminophenol hemisulfate 2-aminophenol sulfate (2:1) (salt)	67845-79-8	158.2	$C_6H_7NO \cdot 1/2\ H_2SO_4$	
p-Aminophenol 4-aminophenol 4-amino-1-hydroxybenzene 4-hydroxy aniline p-hydroxyphenylamine	123-30-8	109.13	C_6H_7NO	
p-Aminophenol hydrochloride 4-aminophenol hydrochloride C.I. 76551	51-78-5	145.52	$C_6H_7NO \cdot HCl$	
p-Aminophenol sulfate 4-aminophenol sulfate o-aminophenol hemisulfate 4-aminophenol sulfate (2:1) (salt)	63084-98-0	158.2	$C_6H_7NO \cdot 1/2\ H_2SO_4$	
m-Aminophenol 3-aminophenol 3-amino-1-hydroxybenzene 3-hydroxyaniline	591-27-5	109.13	C_6H_7NO	

TABLE 1-2

Physical Properties of Selected Aminophenols

Property	o-Aminophenol	o-Aminophenol Hydrochloride	p-Aminophenol	p-Aminophenol Hydrochloride	m-Aminophenol
Description	white crystalline needles[a]	crystalline solid[b]	white to reddish-yellow crystals[c]	white, crystalline powder[a]	white crystals[c]
Melting point	174°C[a]	207°C[a]	189.5-190°C[a]	306°C with decomposition[a]	123°C[a]
Boiling point	sublimes above melting point[d]	NA	sublimes at reduced pressures[a] decomposes (284°C)[b]	NA	NA
Water solubility:		freely soluble[b]		71/100 parts[e], very soluble[b]	
at 0°C	17,000 ppm[d]	1/1.25 parts water[f]	11,000 ppm[d]	1/14 parts water[f]	26,000 ppm[g]
at 13°C	NA	NA	0.39%[b]	NA	NA
at 24°C	NA	NA	0.65%[b]	NA	
at 30°C	NA	NA	0.80%[b]	NA	
at 50°	NA	NA	1.5%[b]	NA	
cold	NA	NA	NA	NA	1/40 parts water[b]
hot	NA	NA	NA	NA	freely soluble[b]
Log octanol/water partition coefficient	0.62[h] 0.52-0.62[d]	NA	0.04[h]	NA	0.17[h] 0.15/0.17[d]
Dissociation constants	pK_2 ~10[i] pK_a=4.84[d] pK_a (20% water-ethanol)=10.29[j]	NA	pK_1=5.50 at 21°C[i] pK_1=5.65 at 25°C[i] pK_2=10.30 at 23°C[i] pK_a (20% water-ethanol)=10.90[j]	NA	pK_a=4.37[i] pK_2=9.8 at 20°C[i] pK_a (20% water-ethanol)=10.37[j]
Nonaqueous solubility:					
alcohol	1 g/23 ml[b]	freely soluble[b]	1.1 g/100 g[g]	soluble[b]	freely soluble[b]
ether	freely soluble[b]	NA	practically insoluble[g]	NA	freely soluble[b]
benzene	very slight [b]	NA	practically insoluble[b]	NA	very slight[b]
methyl ethyl ketone	NA	NA	9.3% (58.5°C)[b]	NA	NA
ethanol	NA	NA	4.5% (0°C)[b]	NA	NA
chloroform	NA	NA	practically insoluble[b]	NA	NA
Vapor pressure at 20°C	NA	NA	0.075 mm Hg[k]	NA	NA

[a]Farris, 1978
[b]Windholz, 1976
[c]Hawley, 1977
[d]Verschueren, 1983
[e]Dean, 1979
[f]Werner, 1947
[g]Perry and Chilton, 1973
[h]Hansch and Leo, 1981
[i]Perrin, 1965
[j]Chuchani and Frohlich, 1971
[k]Weber et al., 1981
NA = Not available

TABLE 1-3

Production Data for Aminophenols*

Company/Location	Manufacturer/Importer	Production Range (lbs/yrs)
o-Aminophenol		
Toms River Chemical Toms River, NJ	manufacturer (not distributed)	confidential
Martin Marietta Corp. Charlotte, NC	manufacturer	confidential
American Hoechst Bridgewater, NJ	importer	confidential
Ashland Chemical Great Meadows, NJ	manufacturer	1000-10,000
Sakai Trading NY New York, NY	importer	none
Rhone-Poulenc Freeport, TX	importer	100,000-1,000,000
Confidential	confidential	confidential
o-Aminophenol Sulfate		
Lowenstein Dyes and Cosmetics Brooklyn, NY	manufacturer	1000-10,000
o-Aminophenol Hydrochloride		
NR	NR	NR
p-Aminophenol		
Alpine Laboratories Bay Minette, AL	manufacturer	0-1000
Proctor Chemical Salisbury, NC	manufacturer	none

TABLE 1-3 (cont.)

Company/Location	Manufacturer/Importer	Production Range (lbs/yrs)
p-Aminophenol (cont.)		
Martin Marietta Corp. Charlotte, NC	manufacturer	confidential
Raleigh Chemical Raleigh, NC	manufacturer	confidential
Confidential	manufacturer	confidential
Marubeni American Corp. Chicago, IL	importer	none
Mobay Chemical Pittsburgh, PA	importer	confidential
American Hoechst Bridgewater, NJ	importer	confidential
Aceto Chemical Flushing, NY	importer	none
AGFA-Gevaett Inc. Teterboro, NJ	importer	none
Sandoz Color and Chemical East Hanover, NJ	importer	none
Sakai Trading NY New York, NY	importer	none
Pettibone-Chicago Inc. Chicago, IL	importer	none
GAF Corp. New York, NY	importer	none
Rhone-Poulenc Inc. Freeport, TX	importer	none

TABLE 1-3 (cont.)

Company/Location	Manufacturer/Importer	Production Range (lbs/yrs)
p-Aminophenol Hydrochloride		
Eastman Kodak Rochester, NY	manufacturer	0-1000
Confidential	manufacturer	confidential
Henkel Inc. Teaneck, NJ	importer	0-1000
p-Aminophenol Sulfate		
Lowenstein and Sons Brooklyn, NY	manufacturer	1000-10,000
m-Aminophenol		
American Cyanamid Bound Brook, NJ	manufacturer (not distributed)	1000-10,000
Henkel Inc. Teaneck, NJ	importer	0-1000
American Hoechst Bridgewater, NJ	importer	confidential
Sandoz Color and Chemical East Hanover, NJ	importer	confidential
Montedison USA New York, NY	importer	confidential
Miles Laboratories Zeeland, MI	importer (not distributed)	10,000-100,000
Hexcel Corp. Zeeland, MI	importer (not distributed)	confidential

*Source: U.S. EPA, 1977

NR = Not reported

importers and production ranges. Importation of o-, m- and p-aminophenol through principal customs districts in the United States in recent years has been reported as follows (USITC, 1982, 1983, 1984b):

	1983 (lbs)	1982 (lbs)	1981 (lbs)
o-aminophenol	87,303	18,078	215,831
m-aminophenol	603,897	564,855	486,324
p-aminophenol	374,892	1,018,195	1,479,177

o-Aminophenol is manufactured by the catalytic hydrogenation of an acetic acid solution of 2-nitrophenol or by the reduction of 2-nitrophenol formed by treating 2-chloronitrobenzene with NaOH (Farris, 1978). p-Aminophenol is manufactured by the Bechamp iron reduction or catalytic hydrogenation of 4-nitrophenol (Farris, 1978). m-Aminophenol is manufactured by the caustic fusion of metanilic acid or by the reduction of 3-nitrophenol (Farris, 1978). The hydrochloride and sulfate salts of the aminophenol isomers are obtained by treating the free base with aqueous HCl or H_2SO_4 solutions.

1.4. USE DATA

o-Aminophenol is used in the dye industry in the manufacture of azo and sulfur dyes and in the photographic industry as a developer, where it is sold under such trade names as Atomal and Ortol (Farris, 1978). In addition, it is used in the oxidative dyeing of furs and hair and in pharmaceuticals (Hawley, 1977; Windholz, 1976). The Food and Drug Administration's Volunteer Cosmetic Registration File lists o-aminophenol as a constituent of 75 products (U.S. EPA, 1984a). The hydrochloride is used in dyeing fur, hair and leather (Windholz, 1976).

p-Aminophenol is widely used as an intermediate in the synthesis of disperse, acid, direct, sulfur, mordant, oxidation and food dyes (Farris, 1978). It also is used as a developer in the photographic industry under trade names such as Activol, Azol, Certinal, Citol, Paranol, Rodinal, Unal and Ursol P (Farris, 1978). Substantial amounts of p-aminophenol are used in the synthesis of the pharmaceutical analgesics, acetaminophen and phenacetin; acetaminophen is known by the trade name Tylenol. p-Aminophenol is also used in various high-performance polymers (Kuney, 1984) and as an anti-oxidant and oil additive (Hawley, 1977). The Food and Drug Administration's Volunteer Cosmetic Registration File lists p-aminophenol as a constituent of 402 products (U.S. EPA, 1984b).

m-Aminophenol is primarily used in the pharmaceutical industry for the synthesis of 4-aminosalicylic acid; it is also used in the dyestuff industry (Farris, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The environmental fate of aminophenols depends upon their ability to undergo chemical, photochemical and biological alterations and to transport or partition from one environmental matrix (air, water, soil-sediment) into another.

2.1. WATER

Pertinent data regarding the hydrolysis of amino phenols were not located in the available literature; however, the chemical structure relationships of o-, m- and p-aminophenol suggest that environmental hydrolysis is not significant.

The chemical oxidation of the aminophenols may be significant in the aquatic media. Based on laboratory studies, Mabey et al. (1981) reported that the alkyl peroxy radical ($RO_2\cdot$) concentration of sunlit natural surface waters may approach 10^{-9} M, with oxidation reactions initiated by $RO_2\cdot$ that include the following:

$$RO_2\cdot + ArOH \rightarrow RO_2H + ArO\cdot$$

$$RO_2\cdot + ArNH_2 \rightarrow RO_2H + ArNH\cdot$$

These two reactions are quite rapid in aquatic environments, having half-lives of less than several days (Mabey et al., 1981). Experimental data specific to aminophenols were not available. The significance of the ability of aminophenols to react with other oxidants in natural waters, such as dissolved oxygen or other radicals formed by sunlight (singlet oxygen, alkoxy radical, hydroxyl radical, etc.) has not been investigated. Since o-Aminophenol and p-aminophenol are rapidly oxidized in air (Farris, 1978), it is likely that oxidation will be significant in natural aquatic media.

The UV absorption spectra for o-, m- and p-aminophenol have been determined (Sadtler, 1961, 1966, n.d.) and show significant absorption in the environmentally important wavelength range of >290 nm. This indicates that direct photolysis can occur in the environment; however, photolysis rate data are not available. Farris (1978) reported that o- and p-aminophenol are unstable to light, which may suggest significant decomposition. Ikekawa et al. (1968) showed that the photolysis of o-aminophenol in organic solvent yields 3-aminophenoxazone at wavelength <300 nm.

The microbial degradation of o-, m- and p-aminophenol has been studied by a number of investigators. Lund and Rodriguez (1984) tested acclimatized activated sludge obtained from a domestic sewage treatment plant in Spain and found that >92% of the initial o- and p-aminophenol concentrations were biodegradable within 26 days, while m-aminophenol was nonbiodegradable. Chambers et al. (1963) found that phenol-acclimated sewage organisms (predominantly Psuedomonas sp.) oxidized o-, m- and p-aminophenol at rates of 138, 249 and 184 $\mu\ell$ O_2 consumed, respectively, after a 180-minute Warburg run, compared with a rate of 365 $\mu\ell$ O_2 consumed for phenol. Using aniline-acclimated activated sludge, 500 ppm test compound and 190-hour Warburg runs, Malaney (1960) found o-, m- and p-aminophenol to have BODT rates of 27, 88 and 69%, respectively. Pitter (1976) used adapted activated sludge tests at 20°C to determine the rate of biological degradation of 123 organic compounds. The percent removed (based on COD) for o-, m- and p-aminophenol were 95.0, 90.5 and 87.0%, respectively, while the rates of biodegradation (mg COD g^{-1} hr^{-1}) in 5 days were 21.1, 10.6 and 16.7, respectively. Haller (1978) found that wastewater sludge obtained from the wastewater treatment plant in Ithaca, NY was unable to degrade m-aminophenol (16 ppm) in test periods >25 days. Beveridge and Tall (1969)

determined that not only were o-, m- and p-aminophenol unable to be used as a sole carbon source by bacterium NCIB 3250 (a member of the Acinetobacter-Moraxella group), but that they were also inhibitory (6-30%) to phenol oxidation by this phenol-adapted bacterium. Kitano (1978) examined the degradation of m-aminophenol (100 ppm) in an activated sludge for 2 weeks and found no biodegradation. The anaerobic degradation of o- and p-aminophenol in lake sediment and in digested municipal sludge was studied by Horowitz et al. (1982); a 29-week incubation period in the lake sediment produced no mineralization and an 8-week incubation period in the sludge produced no mineralization. Zagidullina et al. (1981) reported that m-aminophenol can be biodegraded in wastewaters by adapted microflora from activated sludge with biogenic elements present. Tabak et al. (1964) used phenol-adapted bacteria (Pseudomonas, Achromobacter, Flavobacterium and Xanthomonas mixed cultures) isolated from garden soil, compost, river mud and petroleum wastewater to test the biodegradation of o-, m- and p-aminophenol (100 ppm) in a 180-minute Warburg run; the three isomers were relatively resistant to degradation, having measured BODTs of 15.3, 29.3 and 14.0% for o-, m- and p-aminophenol, respectively. Gerike and Fischer (1979, 1981) tested the biodegradability of m-aminophenol with eight separate test procedures; the tests and the results are summarized in Table 2-1. Novikova et al. (1981) reported that p-aminophenol hydrochloride is bactericidal for sulfate-reducing bacteria.

p-Aminophenol has been shown to be a metabolite that is formed by the microbial decomposition of 4-nitrophenol (Cerniglia et al., 1981; Adhya et al., 1981; Chang et al., 1981; Ferris and Lichtenstein, 1980). It is also a metabolite of the microbial degradation of p-nitroaniline (Udod et al., 1972).

TABLE 2-1

Biodegradability Tests and Results for m-Aminophenol*

Test	Results
Coupled Units (modification of OECD confirmatory test)	94% DOC removal
Zahn-Wellens Test	93% DOC removal (10 days)
Japanese MITI Test	4% DOC removal 0% BODT (14 days)
French AFNOR T90-302 Test	13% DOC removal (28 days) 22% DOC removal (42 days)
CO_2 Evolution Test	0% CO_2 evolution at 25% DOC removal 70% CO_2 evolution at 100% DOC removal
OECD Screening Test	97% DOC removal (19 days)
Closed Bottle Test	1% BODT (30 days)
U.S. EPA Activated Sludge Test	98% DOC removal

*Source: Gerike and Fischer, 1979, 1981

The transport of the aminophenols in the aquatic environment depends upon the ability of the compounds to volatilize, to adsorb to particulate matter and sediment, and to bioaccumulate in aquatic organisms. The volatilization is related to the WS and vapor pressure of a compound. Vapor pressure data are available only for p-aminophenol (0.075 mm Hg at 20°C) (see Section 1.2.). Using this vapor pressure and the available WS data, Henry's Law constant is calculated to be ~10^{-6} atm-m^3/mol, indicating evaporation has little environmental importance. Pertinent data regarding the experimental volatility of the o- and m-aminophenol isomers and of the sulfate and hydrochloride salts were not located in the available literature cited in the Appendix.

The relatively high WS of the aminophenols also suggest that partitioning from the water column into sediment is not likely to be environmentally significant.

Using results from the Japanese MITI test, Kawasaki (1980) reported that the BCF of m-aminophenol is ~10. The BCF of an organic chemical may be estimated from the following equations:

$$\log BCF = 0.76 \log K_{ow} - 0.23 \text{ (Veith et al., 1980)} \qquad (2\text{-}1)$$

$$\log BCF = 2.791 - 0.564 \log WS \text{ (in ppm) (Kenaga and Goring, 1978)} \qquad (2\text{-}2)$$

The log K_{ow} values of o-, m- and p-aminophenol are 0.62, 0.17 and 0.04, respectively (Hansch and Leo, 1981), which correspond to predicted BCFs of 1.7, 0.8 and 0.6, respectively. BCFs of <5 can be predicted from the WSs of

these aminophenols. The WSs of the hydrochloride and sulfate salts predict even lower BCFs. Therefore, these data suggest that bioaccumulation of aminophenols in aquatic organisms is not likely to be significant.

2.2. AIR

The chemical removal processes in the atmosphere include photolytic transformations, reaction with hydroxyl or other radicals and reaction with ozone. Farris (1978) reported that o-aminophenol and p-aminophenol are unstable to air and light, and are rapidly oxidized to brown or black substances. The atmospheric oxidation of o-aminophenol yields phenoxazines. This suggests that o- and p-aminophenol may be quickly removed by chemical and photochemical means when released to the atmosphere. Kinetic rate data for any of the aminophenols under atmospheric conditions are not available. Therefore, atmospheric residence times cannot be predicted. o-Aminophenol, m-aminophenol and p-aminophenol may undergo direct photolysis as they absorb UV radiation >290 nm (Sadtler, 1961, 1966, n.d.). Werner (1947) noted that m-aminophenol is fairly stable to air in contrast to the o- and p-isomers. Stability of the m-isomer towards light has not been reported.

The only physical removal process in the atmosphere that may be important is dissolution. The relatively high WS of the aminophenols may allow the compounds to become dissolved in clouds and raindrops with their subsequent removal by rainfall.

2.3. SOIL

Microbial degradation data presented in Section 2.1. indicate that o-, m- and p-aminophenol can be decomposed biologically under certain aquatic conditions. Alexander and Lustigman (1966) used soil microflora obtained

from a Niagara silt loam to test the decomposition of o- and m-aminophenol as a sole carbon source at 25°C; the o-aminophenol decomposed in 4 days, while the m-aminophenol was not degraded after 64 days. Haller (1978) found that Windsor loamy fine sand soil was unable to degrade m-aminophenol (16 ppm) in test periods >25 days. Walker and Harris (1969) found that a Pseudomonas sp., isolated from soil and adapted to aniline, was able to oxidize p-aminophenol.

Sonawane and Knowles (1971) examined the degradation of m-aminophenol in soil under laboratory conditions. Soil (pH=8.0 and organic matter content =0.9%) was collected near Hartsburg, MO, and placed in Mason jars where the moisture was adjusted to 20%. m-Aminophenol (0.2 ppm) was thoroughly mixed into the soil, and the soil was analyzed after 0, 4, 8 and 16 days. After 16 days, 37% of the m-aminophenol had degraded; the degradation products were not identified nor were the degradation processes determined. The authors also found that the soil degradation of the herbicide phenmedipham yielded m-aminophenol as one of the metabolites.

p-Aminophenol and o-aminophenol are readily oxidized in air (Farris, 1978); therefore, these compounds are not likely to persist under aerobic soil conditions. In addition, the direct photolysis or photosensitized photolysis of o-, m- and p-aminophenol from soil surfaces may be important.

The sorption of m-aminophenol from aqueous solutions by Na-kaolinate and Na-montmorillonite clays was examined in the laboratory by Luh and Baker (1970). m-Aminophenol was weakly sorbed or not sorbed at all at pH 7 within a 120-hour time frame, and showed no sorption at all at pH 10. It exhibited

some positive sorption over the acidic pH range. The K_{oc} of an organic compound can be estimated from WS-K_{ow} data by using the following equations:

$$\log K_{oc} = 3.64\text{-}0.55 \log WS \text{ (in ppm) (Kenaga and Goring, 1978)} \quad (2\text{-}3)$$

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \text{ (Kenaga and Goring, 1978)} \quad (2\text{-}4)$$

Log K_{ow} and WS data available for o-, m- and p-aminophenol result in calculated K_{oc} values of $\leq$52, indicating that the aminophenols are highly mobile in soil and can, therefore, be easily leached. The high WS of the hydrochloride and sulfate salts also predict significant leachability.

Lack of experimental data regarding the soil volatility of the aminophenols precludes consideration of soil volatility of the aminophenols.

2.4. SUMMARY

The instability of o-aminophenol and p-aminophenol to light and air, coupled with their reported ability to be biodegraded by various microorganisms and conditions, suggest that these compounds will not persist for long periods of time in the environment. Their removal from water and soil may be slowed by dark and anaerobic conditions. m-Aminophenol is more stable to air than the o- and p-isomers, but it is susceptible to direct photolysis; the rate of photolysis has not been determined. Its biodegradation by various microorganisms and conditions has also been documented. The relative resistance of m-aminophenol to both chemical oxidation and biodegradation may make it more persistent in the environment than o-aminophenol and p-aminophenol.

In the aquatic environment, chemical oxidation, photolysis and microbial degradation may all be important removal mechanisms for the aminophenols; kinetic rate data are not available. Volatilization, partitioning into sediments or bioaccumulation are not likely to be important in the aquatic media. In the atmosphere, the oxidation of o-aminophenol and p-aminophenol by air and light will, likely, remove these compounds rapidly. In the soil, o-, m- and p-aminophenol are susceptible to microbial decomposition; however, the significance of this removal mechanism is dependent upon the localized soil conditions. Chemical oxidation and surface photolysis may also be important. It can be predicted that the aminophenols are readily leachable from soil.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base contains no observations for any of the aminophenols being considered. Shackelford and Keith (1976) reported the detection of aminophenol (isomer and concentration not reported) in three effluents from chemical plants in Kingsport and Morristown, TN, during September, 1974. Aminophenols have also been detected in surface waters of the Rome Province in Italy (Sanna et al., 1983).

3.2. FOOD

Pertinent data regarding the exposure of aminophenols in food were not located in the available literature cited in the Appendix.

3.3. INHALATION

Pertinent data regarding exposure or monitoring of aminophenols in ambient air were not located in the available literature cited in the Appendix.

3.4. DERMAL

o-Aminophenol is listed as a constituent of 75 products and p-aminophenol is listed as a constituent of 402 products by the FDA's Volunteer Cosmetic Registration file (U.S. EPA, 1984a,b). In addition, o-, m- and p-aminophenol have been identified in commercial hair dye shampoos and solutions (Liem and Rooselaar, 1981) and in oxidative hair dyes (Kijima et al., 1983). Therefore, dermal exposure is possible from various cosmetic products.

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism and/or excretion of p-aminophenol sulfate, o-aminophenol hydrochloride or o-aminophenol sulfate were not located in the available literature cited in the Appendix.

4.1. ABSORPTION

Bray et al. (1952) administered o-, m- or p-aminophenol to rabbits at a single oral dose of 1 g/rabbit and collected urine for 24 hours. Recovery in urine of the administered dose as unchanged compound and metabolites was 95% for o-aminophenol, 78% for m-aminophenol and 87-100%, for p-aminophenol. These results indicate that the aminophenols were extensively absorbed from the gastrointestinal tract.

Application of ^{14}C-p-aminophenol to the backs of hairless rats at 15 μg/cm^2 resulted in the excretion of 1.0±0.22 μg of radiolabeled material in the urine and 0.53±0.24 μg of radiolabeled material in the feces within 96 hours of dosing (Tsomi and Kalopissis, 1982). Increasing the amount of ^{14}C-labeled p-aminophenol applied cutaneously to 75 μg/cm^2 resulted in the urinary excretion of 3.26±0.27 μg, and the fecal excretion of 2.0±0.50 μg of radioactive material within 96 hours of dosing. Application of 375 μg/cm^2 of ^{14}C-p-aminophenol did not result in increased amounts of radioactive compounds in the 96-hour samples of urine (3.5±0.34 μg) and feces (2.0±0.53 μg). Although Tsomi and Kalopissis (1982) reported that "for all practical purposes [dyestuffs; i.e., p-aminophenol] do not cross the cutaneous barrier," it is apparent that some percutaneous absorption occurred in the hairless rat.

Pertinent data regarding the absorption of p-aminophenol hydrochloride were not located in the available literature cited in the Appendix.

4.2. DISTRIBUTION

Two hours after the injection of four male Sprague-Dawley rats with 2.1 mmol/kg of H^3-p-aminophenol hydrochloride in the tail vein, H^3-p-aminophenol was recovered from the kidney (344.08 nmol/mg protein), from the liver (186.03 nmol/mg protein) and from the plasma (30.52 nmol/mg protein) (Crowe et al., 1979). Of these concentrations of H^3-p-aminophenol, 20% was bound to protein in the kidney, 1.9% was bound to protein in the liver and 3.6% was bound to plasma protein.

Pertinent data regarding the distribution of p-aminophenol or m-aminophenol were not located in the available literature cited in the Appendix.

4.3. METABOLISM

In the previously described study of Bray et al. (1952), rabbits were treated by gavage with o-, m- or p-aminophenol at a dose of 1 g/rabbit and the urine excreted over 24 hours was analyzed for metabolites. The percentages of the administered dose recovered as unchanged parent compound and as metabolites are presented in Table 4-1.

According to Fairhall (1969), only 8% of the oral dose of p-aminophenol was excreted as p-aminophenylglucuronide in the urine of rabbits.

Nakao et al. (1958) compared the metabolic products of m-aminophenol found in the 24-hour urine of dogs, rabbits and mice following oral or intraperitoneal treatment of the animals. The protocol of the experiment was unclear. The urine of dogs contained m-aminophenol sulfate, m-aminophenyl glucuronide and an unidentified metabolite. The urine of rabbits and mice contained N-acetyl-m-aminophenol, N-acetyl-m-aminophenol sulfate, m-aminophenol sulfate, N-acetyl-m-aminophenyl glucuronide, m-aminophenyl glucuronide and the unidentified metabolite.

TABLE 4-1

Percentage of Administered Dose Recovered from the 24-Hour Urine of Rabbits Treated Orally with Aminophenols*

Metabolite	o-Aminophenol	m-Aminophenol	p-Aminophenol
Unchanged aminophenol	11	0	2
Acetamidophenol	2-4	12-19	13-25
Aminophenolsulfate	15	0	8
Acetamidophenolsulfate	0	15	4
Aminophenylglucuronide	52	59	45
Acetamidophenylglucuronide	13	5	16

*Source: Bray et al., 1952

After a single intravenous injection of 2 mmole/kg of p-aminophenol hydrochloride into female hooded rats, free p-aminophenol, N-acetyl-p-aminophenol, and a nonacetylated conjugated product were identified in the urine (Calder et al., 1971).

Intravenous administration of p-aminophenol hydrochloride to groups of male and female Sprague-Dawley rats resulted in nephrotoxicity, which was inconsistently affected by inducers and/or inhibitors of microsomal mixed function oxidases (Calder et al., 1979). Calder et al. (1979) concluded that the kidneys, metabolized p-aminophenol by biological oxidation systems other than the mixed function oxidase system and by autooxidation to a reactive intermediate metabolite responsible for the nephrotoxic effects. Since p-aminophenol had relatively little effect on the liver, (Calder et al. (1979) suggested that levels of the toxic intermediate produced in the liver were below the threshold concentration for cell necrosis.

4.4. EXCRETION

As discussed previously in Sections 4.1. and 4.3., Bray et al. (1952) recovered 95, 78 and 87-100% of the orally administered dose of o-, m- and p-aminophenol, respectively, from the 24-hour urine of rabbits. The percentages of unchanged parent compound and metabolites were presented in Table 4-1.

5. EFFECTS

5.1. CARCINOGENICITY

As reviewed in IARC (1974), administration of diets containing 0.09-0.2% p-aminophenol or o-aminophenol hydrochloride to groups of 12-15 rats for 270-341 days did not result in any increased incidence of tumors (Ekman and Strombeck, 1949a,b; Miller and Miller, 1948).

To test the carcinogenicity of o-aminophenol, Clayson et al. (1958) implanted cholesterol-based pellets containing o-aminophenol into the urinary bladder of 37 albino mice. A control group of 55 mice received the cholesterol pellets without any added chemical. The mice were killed after 25 weeks. The incidence of squamous metaplasia (7/37) and of carcinomas (2/37) in the o-aminophenol-treated group was not significantly different from the incidence of squamous metaplasia (7/55) and of carcinomas (5/55) in the control group (Clayson et al., 1958) (Table 5-1).

In an abstract of a German study lacking substantial information, Boyland (1960) stated that bladder cancer in mice was caused by the appearance of o-aminophenol in the urine of mice treated with various aromatic amines.

Additional pertinent data regarding the carcinogenicity of o-aminophenol, o-aminophenol hydrochloride, o-aminophenol sulfate, m-aminophenol, p-aminophenol, p-aminophenol hydrochloride or p-aminophenol sulfate were not located in the available literature cited in the Appendix.

5.2. MUTAGENICITY

As indicated in Table 5-2, p-aminophenol was not mutagenic in assays conducted with Salmonella typhimurium or Escherichia coli. The only exception is the report by Wild et al. (1980), as summarized by the U.S. EPA (1984b), in which p-aminophenol was positive for reverse mutation in S.

TABLE 5-1

Animal

Agent: o-Aminophenol[a]

Exposure Route	Species/ Strain	Sex	Dose (mg/kg/day)	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Implant[b]	mice	NR	NR	25 weeks	25 weeks	"purified by sublimation"	cholesterol pellet	urinary bladder	epithelial carcinoma	2/37 (p-n.s.)
	mice	NR	control[c]	25 weeks	25 weeks	NA	cholesterol pellet	urinary bladder	epithelial carcinoma	5/55

QUALITY OF EVIDENCE

Strengths of Study: The study was designed to test the contribution of o-aminophenol, a metabolite of several xenobiotics (Section 5.1.), on the induction of bladder tumors. Implantation directly into the bladder was performed to mimic the deposition of o-aminophenol in the bladder following metabolism of the xenobiotic.

Weakness of study: The study introduces the confounding factor of the effect of cholesterol pellets.

Overall adequacy: Inadequate

[a]Source: Clayson et al., 1958

[b]Exposure was maintained by introducing cholesterol pellets containing o-aminophenol into the urinary bladder.

[c]Control mice received cholesterol pellets without any added chemical.

NR = Not reported; NA = not applicable

TABLE 5-2

Mutagenicity of p-Aminophenol

Assay	Indicator/ Organism	Strain/ Cell Line	Concentration/ Dose	Application Method	Metabolic Activation	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium	TA98 TA100 TA1535 TA1537	up to 500 µg/plate	plate incorporation	+/- S9	-/-	NC	McCann et al., 1975
Reverse mutation	S. typhimurium	TA98	15, 50 or 150 µg/plate	plate incorporation	+/- S9	-/-	NC	Yoshikawa et al., 1976
Reverse mutation	S.typhimurium	TA1538	50 or 100 µg/plate	plate incorporation	+/- S9	-/-	NC	Garner and Nutman, 1977
Reverse mutation	S. typhimurium	TA98 TA100	NR	plate incorporation	+ S9	-	S-9 was obtained from hamsters	Savamura et al., 1978
Reverse mutation	S. typhimurium	TA98 TA100	0.5, 1.0 or 2.0 µmol/plate	plate incorporation	+/- S9	-/-	NC	Degawa et al., 1979
Reverse mutation	S. typhimurium	TA98 TA100	25-500 µg/plate	plate incorporation	+/- S9	-/-	NC	Lavoie et al., 1979
Reverse mutation	S. typhimurium	TA1535	0.2-2.5 µmol/plate	plate incorporation	+/- S9	-/+	NC	Wild et al., 1980
Reverse mutation	S. typhimurium	TA98 TA100 TA1535 TA1537 TA1538	NR	plate incorporation	+/-	-/-	NC	Deflora et al., 1984
Forward mutation	Escherichia coli	GY5027 (lysogen) GY4015 (indicator)	up to 2000 µg/plate	plate incorporation	+/- S9	-/-	The assay involved evaluation of prophage inducing activity. This group also reported that p-aminophenol was not mutagenic in the E. coli rec assay or in the S. typhimurium assays, but did not report any details.	Mamber et al., 1984
Rec assay	E. coli	WP2 WP100	up to 2000 µg/plate	liquid incubation	+ S9	-	NC	Mamber et al., 1983

0659p
06/26/85

TABLE 5-2 (cont.)

Assay	Indicator/ Organism	Strain/ Cell Line	Concentration/ Dose	Application Method	Metabolic Activation	Response	Comments	Reference
Forward mutation	mouse lymphoma cells	L5178Y/ TK	0-7 µg/mL	cell culture	- S9	+	There was a dose-related increase in mutation frequency.	Oberly et al., 1984
Forward mutation	mouse lymphoma cells	L5178Y/ TK	0-19.2 µg/mL	cell culture	+ S9	+	There was a dose-related increase in mutation frequency.	Amacher and Turner, 1982
SCE	human lymphocytes	NA	10^{-7} M 10^{-6} M 10^{-5} M 10^{-4} M	cell culture	+ S9 + S9 + S9 + S9	- - - +	NC	Takehisa and Kanaya, 1982
SCE	Chinese hamster cells	V79	$0.5\text{-}2.0\times10^{-5}$ M	cell culture	NR	+	Data were reported in an abstract.	Wild et al., 1981
SCE	human fibroblasts	GM-3468	0.005-0.2 mM	cell culture	NR	-	p-Aminophenol is cytotoxic and inhibits cell cycle progression o-aminophenol produced SCEs	Wilmer et al., 1981
Unscheduled DNA synthesis	rat hepatocytes	NA	≤100 nmol/mL	cell culture	+/-	-/-	NC	Probst et al., 1981
Inhibition of DNA synthesis	human lympho-blastoid cells	EBV-transformed	0-2 mM	cell culture	none	+	Dose-related inhibition	Hayward et al., 1982
Chromosome breaks	mouse bone marrow cells	NA	0.25 or 0.50 mL of 0.01 or 0.02 M	i.p. injection	NA	+	NC	Mitra and Manna, 1971
Micronucleus test	rat bone marrow cells	NA	3200 mg/kg	oral	NA	-	NC	Hossack and Richardson, 1977
Micronucleus test and sperm-head abnormality test	mouse bone marrow cells or sperm	NA	0.5-2.0 mmoles/kg	i.p. injection	NA	+	NC	Wild et al., 1981

NC = No comment; NR = not reported

0657p 06/26/85

typhimurium strain TA1535 when incubated in the absence, but not in the presence, of an exogenous metabolic activator. p-Aminophenol produced a dose-related increase in forward mutations in mouse lymphoma cells in vitro, both in the presence (Amacher and Turner, 1982) and the absence (Oberly et al., 1984) of metabolic activation. Positive results were obtained for SCE in Chinese hamster cells and human lymphocytes (Wild et al., 1981; Takehisa and Kanaya, 1982), but Wilmer et al. (1981) reported that p-aminophenol did not produce SCE in human fibroblasts. These authors did find that p-aminophenol was cytotoxic and inhibited cell cycle progression. Unscheduled DNA synthesis in rat hepatocytes in vitro was not affected by p-aminophenol (Probst et al., 1981).

Hayward et al. (1982) reported that p-aminophenol caused a dose-related inhibition of DNA synthesis in human lymphocytes in vitro. Mitra and Manna (1971) reported that p-aminophenol caused chromosome breaks in bone marrow cells removed from mice 24 hours after intraperitoneal injection of p-aminophenol. p-Aminophenol was negative in the micronucleus test in rats treated by gavage with a total dose of 3200 mg/kg of p-aminophenol (Hossack and Richardson, 1977), but positive responses in the micronucleus test and the abnormal sperm-head test were obtained after mice were treated intraperitoneally with 0.5-2.0 mmoles/kg (Wild et al., 1981).

As indicated in Table 5-3, m-aminophenol was negative for reverse mutations in S. typhimurium strains TA98 and TA100 with and without metabolic activation when tested by plate incorporation (Lavoie et al., 1979). The frequency of SCE in Chinese hamster cells was not affected by m-aminophenol (Wild et al., 1981). Intraperitoneal injection of mice with 0.5-2.0 mmol/kg of m-aminophenol did not result in an increased incidence of micronuclei in

TABLE 5-3

Mutagenicity of m-Aminophenol

Assay	Indicator Organism	Strain/ Cell Line	Concentration/ Dose	Application Method	Metabolic Activation	Response	Comments	Reference
Reverse mutation	Samonella typhimurium	TA98 TA100	25-500 µg	plate incorporation	+/-	-	NC	Lavoie et al., 1979
SCE	Chinese hamster cells	V79	0.5-2.0x10^{-3} M	cell culture	NR	-	Information taken from an abstract.	Wild et al., 1981
Micronucleus test	rat bone marrow cells	NA	5000 mg/kg	oral	NA	-	NC	Hossack and Richardson, 1977
Micronucleus test and sperm-head abnormality test	mouse bone marrow cells or sperm	NA	0.5-2.0 mmoles/kg	i.p. injection	NA	-	NC	Wild et al., 1981

NC = No comment; NR = not reported

bone marrow cells or in a positive response in the sperm-head abnormality test (Wild et al., 1981). Administration of 5000 mg/kg to rats by gavage in two equal doses separated by a 24-hour interval resulted in the death of 3 of 10 rats, but no increase in the incidence of micronucleated polychromatic erythrocytes (Hossack and Richardson, 1977).

In an abstract, Watanabe et al. (1980) reported that the mutagenicity of toluene-2,5-diamine HCl in S. typhimurium strain TA1538 was decreased, but the mutagenicity of p-nitro-o-phenylenediamine was increased by m-aminophenol.

As indicated in Table 5-4, o-aminophenol was mutagenic in S. typhimurium strain 100 in three (NTP, 1983; Lavoie et al., 1979; Nishimura and Oshima, 1983) of six (Degawa et al., 1979; Yoshikawa et al., 1976; DeFlora et al., 1984) bacterial assays. In two of the assays (NTP, 1983; Nishimura and Oshima, 1983), o-aminophenol was mutagenic both in the presence and absence of exogenous metabolic activation. In the third assay (Lavoie et al., 1979), o-aminophenol was weakly positive only in the presence of metabolic activation.

o-Aminophenol was negative in a sex-linked recessive lethal mutation assay in Drosphila melanogaster conducted by NTP (1983). Wild et al. (1981) found that o-aminophenol was positive, while Kirchner and Bayer (1982) reported negative results for SCE in Chinese hamster cells. o-Aminophenol treatment increased the incidence of SCE in cultured human fibroblasts (Wilmer et al., 1981) and cultured human lymphocytes (Kirchner and Bayer, 1982).

In an abstract, Wild et al. (1981) reported that o-aminophenol was positive in the mouse bone marrow micronucleus test and the sperm-head abnormality test.

TABLE 5-4

Mutagenicity of o-Aminophenol

Assay	Indicator Organism	Strain/ Cell Line	Concentration/ Dose	Application Method	Metabolic Activation	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium	TA98 TA100 TA1535 TA1537	100-1000 µg/plate	plate incorporation	+/-	see comment	A positive response was obtained in strain TA100 both with and without metabolic activation. A negative response was obtained in the other strains regardless of the presence or absence of metabolic activation.	NTP, 1983
Reverse mutation	S. typhimurium	TA98 TA100	0.5-2.0 µmol/plate	plate incorporation	+/-	-/-	NC	Degawa et al., 1979
Reverse mutation	S. typhimurium	TA98 TA100	15-150 µg/plate	plate incorporation	+/-	-/-	NC	Yoshikawa et al., 1976
Reverse mutation	S. typhimurium	TA98 TA100	25-500 µg/plate	plate incorporation	+/-	+/-	Weakly positive with metabolic activation in strain TA100, but not in strain TA98.	Lavoie et al., 1979
Reverse mutation	S. typhimurium	TA98 TA100 TA1535 TA1537 TA1538	NR	plate incorporation	+/-	-/-	NC	Deflora et al., 1984
Reverse mutation	S. typhimurium	TA98 TA100	NR	NR	+/-	+/+	The abstract reported that the mutagenic activity of o-aminophenol was 2-3 times greater than controls.	Nishimura and Oshima, 1983
Recessive lethal	Drosophila melanogaster	NR	NR	NR	NA	-	NC	NTP, 1983
Micronucleus test and sperm-head abnormality test	mouse bone marrow cells or sperm	NA	0.5-2.0 mmole/kg	i.p. injection	NA	+	NC	Wild et al., 1981

TABLE 5-4 (cont.)

Assay	Indicator Organism	Strain/ Cell Line	Concentration/ Dose	Application Method	Metabolic Activation	Response	Comments	Reference
SCE	Chinese hamster bone marrow cells	NA	NR	cell culture	NR	-	NC	Kirchner and Bayer, 1982
SCE	Chinese hamster cells	V79	0.5-2.0x10^{-5} M	cell culture	NR	+	Information was taken from an abstract.	Wild et al., 1981
SCE	human fibroblasts	GM-3468	0.01-0.3 mM	cell culture	NR	+	The significance of the increase was at the 0.05 level.	Wilmer et al., 1981
SCE	human lymphocytes	NA	NR	cell culture	NR	+	NC	Kichner and Bayer, 1982

NC = No comment; NR = not reported

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Pertinent data regarding the mutagenicity of p-aminophenol sulphate, p-aminophenol hydrochloride, o-aminophenol sulphate and o-aminophenol hydrochloride were not located in the available literature cited in the Appendix.

5.3. TERATOGENICITY

Groups of 35 female Sprague-Dawley rats were exposed to diets containing 0, 0.13, 0.25 or 0.98% m-aminophenol for 13-14 weeks, at which time 25 of the rats were mated with untreated males (Re et al., 1984). Ten rats from each of the original groups had been killed and necropsied at 13 weeks (Section 5.5.). Treatment of mated rats was continued at the original levels until the rats were killed on day 20 of gestation. Body weight gain during pregnancy was significantly less than controls only in the high-dose group, but the mid- and high-dose groups had significantly reduced body weight during the pre-mating exposure period. Food consumption was also significantly less only in the high dose group during gestation. No other signs of maternal toxicity were observed in the groups treated during gestation; however, treatment-related effects were observed in the mid- and high-dose groups during the pre-mating exposure period and at necropsy (Section 5.5.). The incidence of fetal mortality, malformations and resorptions was not significantly higher in the treated animals than in the controls. Although there appeared to be a decreased number of implantation sites and of corpora lutea at the middle- and high-dose levels, the decrease was not statistically significant (Re et al., 1984).

Groups of Syrian golden hamsters received 0 (n=6), 100 (n=2) or 200 (n=3) mg/kg of p-aminophenol by gavage on day 8 of gestation (Rutkowski and Ferm, 1982). The dams were killed on day 13 of gestation by carbon dioxide induced anoxia. As indicated in Table 5-5, no effect on the number of resorptions or the incidence of any malformation was reported.

TABLE 5-5

Teratogenicity of o-, m- and p-Aminophenol in Syrian Golden Hamsters[a,b,c]

Route of Administration	Compound	Dose (mg/kg)	Total No. of Litters	Total No. of Fetuses	Total No. of Resorptions	Total No. of Fetuses with Malformations	No. of Resorptions/No. of Implantations	No. of Litters with One or More Malformed Fetuses/ No. of Litters	No. of Malformed Fetuses/No. of Fetuses
Oral	p-aminophenol	0	6	83	3	0	3.5	0	0
		100	2	22	2	0	8.3	0	0
		200	3	37	2	0	5.1	0	0
Intraperitoneal	p-aminophenol	0	6	62	7	1	10.1	16.7	1.6
		100	22	262	23	19	8.1	36.4	7.3
		150	9	104	9	24	8.0	66.7	23.1
		200	26	214	106	130	33.1	92.3	60.8
	o-aminophenol	100	7	80	5	7	5.9	14.3	8.8
		150	7	68	20	44	22.7	85.7	64.7
		200	7	41	56	41	57.7	100	100
	m-aminophenol	0	4	48	3	0	5.9	0	0
		100	2	26	2	0	7.1	0	0
		150	6	84	3	6	3.4	16.7	7.1
		200	5	50	4	0	7.4	0	0
Intravenous	p-aminophenol	0	7	88	4	1	4.3	14.3	1.1
		100	12	145	19	25	11.6	50.0	17.2
		150	8	70	36	40	35.3	87.5	57.1
		200	5	28	42	25	60.0	100	89.3
		250	3	3	33	3	91.7	100	100

[a]Source: Rutkowski and Ferm, 1982

[b]The dosing of the hamsters was performed on day 8 of gestation. The dams were killed on day 13 of gestation.

[c]The p-, o- and m-aminophenol were administered in a 10% aqueous solution of DMSO, which was reported to be a non-teratogenic level of DMSO for hamsters (Ferm, 1966).

Groups of Syrian golden hamsters received 0 (n=6), 100 (n=22), 150 (n=150) or 200 (n=26) mg/kg of p-aminophenol by intraperitoneal injection on day 8 of gestation (Rutkowski and Fern, 1982). The dams were killed on day 13 of gestation. As indicated in Table 5-5, the incidence of resorp- tions and malformations increased significantly in a dose-related manner ($p<0.01$). Similarly, intraperitoneal administration of o-aminophenol at doses of 100 (n=7), 150 (n=7) and 200 (n=7) mg/kg on day 8 of gestation resulted in a significantly ($p<0.01$) increased incidence of malformations and resorptions, observed when the dams were sacrificed on day 13 of gestation. When m-aminophenol was administered intraperitoneally at doses of 100 (n=2), 150 (n=6) and 200 (n=5) mg/kg on day 8 of gestation, no dose-related effect was observed in the incidence of resorptions or malformations (see Table 5-5).

Intravenous injection of the sublingual vein of pregnant hamsters on day 8 of gestation with 0 (n=7), 100 (n=12), 150 (n=8), 200 (n=5) or 250 (n=3) mg/kg of p-aminophenol resulted in a significant increase in the incidence of malformations and resorptions by day 13 of gestation (see Table 5-5).

As indicated in Table 5-6, the types of malformations induced by the intraperitoneal and intravenous administration of p-aminophenol and by the intraperitoneal injection of o-aminophenol appeared to be dose-related and included neural defects (spina bifida, exencephaly and encephalocele), eye defects (microphthalmia and anophthalmia), umbilical herniation (sometimes including eventration of the abdominal viscera), rib defects and limb defects. Ectopic heart was observed twice and cleft palate, occult cranioschisis and abnormal genitalia were each observed once (Rutkowski and Ferm, 1982).

TABLE 5-6

Types and Incidence of Malformations in the Syrian Golden Hamster Treated with o-, m- or p-Aminophenol*

Malformation	Dose (mg/kg)	Route of Administration		
		i.p.	i.v.	po
Neural tube defects	0	0/0	1/1	0/0
	100	9/5	7/3	0/0
	150	11/3	15/6	NT
	200	95/21	15/4	0/0
Eye defects	0	0/0	0/0	0/0
	100	5/2	13/5	0/0
	150	11/4	24/7	NT
	200	75/22	12/3	0/0
Limb defects	0	1/1	0/0	0/0
	100	3/2	5/3	0/0
	150	4/2	17/5	NT
	200	74/17	17/3	0/0
Rib defects	0	0/0	0/0	0/0
	100	5/1	0/0	0/0
	150	1/1	0/0	NT
	200	29/11	1/1	0/0
Tail defects	0	0/0	0/0	0/0
	100	5/3	3/2	0/0
	150	4/3	4/3	NT
	200	24/7	11/5	0/0
Umbilical hernias	0	0/0	0/0	0/0
	100	3/3	1/1	0/0
	150	1/1	8/3	NT
	200	44/14	7/2	0/0

*Source: U.S. EPA, 1984b

i.p. = Intraperitoneal; i.v. = intravenous; po = per os, by gavage; NT = not tested

The topical application of 2 mg/kg of hair dye formulations (several of which contained p-, m- and/or o-aminophenol in a concentration ranging from 0.02-1.0%) to the skin of pregnant CD rats on days 1, 4, 7, 10, 13, 16 and 19 of gestation produced no embryotoxic or teratogenic effects (Burnett et al., 1976).

Pertinent data regarding the teratogenicity of p-aminophenol hydrochloride, p-aminophenol sulfate, o-aminophenol hydrochloride and o-aminophenol sulfate were not located in the available literature cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

With the exception of sperm morphology studies, pertinent data regarding other reproductive effects of p-aminophenol, p-aminophenol hydrochloride, p-aminophenol sulfate, m-aminophenol, o-aminophenol, o-aminophenol hydrochloride or o-aminophenol sulfate were not located in the available literature.

Groups of five male mice received intraperitoneal injections of 0, 25, 50, 125, 200, 250, 300, 400 or 500 mg/kg of p-aminophenol for 5 consecutive days (Topham, 1980). Five weeks after the last dose the mice were killed, and the sperm from the cauda epididymis were evaluated. An increased number of abnormally shaped sperm heads were observed in the mice treated with p-aminophenol (Topham, 1980). The sperm abnormalities persisted for 26 weeks after treatment (Topham and Scott, 1981). As reported in an abstract, ingestion of a dose level that approaches the MTD of p-aminophenol by male mice on a daily basis resulted in small or undetected changes in sperm head shape after 2, 4, 5, 6, 8, 12 and 13 weeks of exposure (Topham and Scott, 1981).

Wild et al. (1981) reported in their abstract that o- and p-aminophenol, but not m-aminophenol, were positive in the sperm-head abnormality test in mice treated intraperitoneally with the compounds at 0.5-2.0 mmoles/kg.

5.5. CHRONIC TOXICITY

Groups of 35 female Sprague-Dawley rats were exposed to diets containing 0, 0.13, 0.25 or 0.98% of m-aminophenol (Re et al., 1984). After 13 weeks of feeding, 10 females from each group were killed, weighed and prepared for complete evaluation; the remaining 25 female rats in each group were used in a teratogenicity study described in Section 5.3. The level of significance was set at $p<0.05$ for all parameters. No effects on clinical chemistry parameters were reported. At the highest dose tested (0.98% m-aminophenol), the hemoglobin level and the red blood cell count were significantly decreased, while the mean corpuscular volume was significantly increased. The body weights of the rats in the middle (0.25% m-aminophenol) and high (0.98% m-aminophenol) dose groups were significantly less than controls. Food consumption in the high-dose group was also consistently significantly less than that of controls, and food consumption in the middle-dose group was occasionally significantly less than that of controls. The absolute and relative weight of the thyroid gland in the low- (0.1% m-aminophenol) and mid- (0.25% m-aminophenol) dose groups was significantly less than the thyroid weight of controls; whereas, the relative weight of the thyroid glands in the high-dose (0.98% m-aminophenol) group was significantly greater than that of controls. Increased epithelial cell height and reduced follicular size were observed in the thyroids of the rats in the middle- and high-dose group. The histology of the thyroids in the low-dose group was similar to controls. Deposition of iron-positive pigment was found in

the renal tubules of 1/10, 2/10, 1/10 and 8/10 rats of control, low-, middle- and high-dose groups, respectively, and in the liver of 3/10, 2/10, 2/10 and 8/10 rats in the control, low-, middle- and high-dose groups, respectively. The amount of iron-positive pigment in the spleen was reported to increase in a dose-related manner (Re et al., 1984).

Pertinent data regarding the chronic or subchronic toxicity of p-aminophenol, p-aminophenol hydrochloride, p-aminophenol sulfate, o-aminophenol, o-aminophenol hydrochloride or o-aminophenol sulfate were not located in the available literature cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

The literature contains abundant relevant information concerning the effects of acute treatment with aminophenols. An indication of acute toxicity of the various aminophenols can be obtained from the listing of the LD_{50} values in Table 5-7. Following acute administration to animals by subcutaneous, intravenous and oral routes, aminophenols have been reported to cause nephrotoxicity (Calder et al., 1971; Newton et al., 1983 a,b,c; Cottrell et al., 1976; Crowe et al., 1977a,b; Gyrd-Hansen, 1974; Tange et al., 1977), methemoglobin formation (Miller and Smith, 1970; Fraser and Vesell, 1968; Wind and Stern, 1977; Harrison and Jollow, 1981) and convulsions (Angel and Rogers, 1972). The interaction of various cytoplasmic enzymes with p-aminophenol (Wishart and Dutton, 1976, 1977; Wishart et al., 1977; Scragg et al., 1983; Dybing and Rugstad, 1972; Rugstad and Dybing, 1974; Kachole et al., 1978; Bergheim et al., 1973; Von Bruchhausen and Baumann, 1982; Baumann et al., 1983a,b; Andersson et al., 1982; Josephy et al., 1983; Hargreaves, 1968; Neish, 1967) has been described. The administration of a variety of compounds such as 3-acetamidophenol, nitrobenzene, aniline, phenylhydroxylamine and acetominophen has resulted in the formation

TABLE 5-7

Lethality of the Aminophenols

Compound	Species	Route	LD_{50} (mg/kg)	Reference
p-Aminophenol	rat	oral	671	Lloyd et al., 1977
p-Aminophenol	rat	oral	1270	Lloyd et al., 1977; NIOSH, 1974
p-Aminophenol	rat	oral	375	Lewis and Tatken, 1982
p-Aminophenol	mouse	oral	420	Lewis and Tatken, 1982
p-Aminophenol	rabbit	dermal	>8000	Mallinckrodt, Inc., 1983
p-Aminophenol hydrochloride	mouse	intravenous	700	Kiese and Rachor, 1964
m-Aminophenol	rat	NR	1000	Lloyd et al., 1977
m-Aminophenol	rat	NR	812	Clairol, n.d.
m-Aminophenol	rabbit	intravenous	500	Ozawa et al., 1956
m-Aminophenol	mouse	intravenous	340.7	Ozawa et al., 1956
o-Aminophenol	rat	oral	1300	Lewis and Tatken, 1982
o-Aminophenol	mouse	intraperitoneal	200	Lewis and Tatken, 1982
o-Aminophenol hydrochloride	mouse	intravenous	460	Kiese and Rachor, 1964

NR = Not reported

of one or several of the aminophenols as a terminal or intermediate metabolite (Quitmann et al., 1984; Rickert et al., 1983; Eyer et al., 1980; Stevens et al., 1980; Chhabra et al., 1972; Boobis and Powis, 1975; Kao et al., 1978; Irons et al., 1980; Carpenter and Mudge, 1981; Newton et al., 1982, 1983a,b,c). Short-term tests have indicated that p-aminophenol was not toxic to rats when administered by inhalation or rabbits by intraoccular application (Mallinckrodt, Inc., 1983).

Newton et al. (1982) treated male Fischer 344 rats with a single oral dose of p-aminophenol at 0, 50, 100, 150 or 200 mg/kg. The rats were killed 24-18 hours later. At $\geq$100 mg/kg, BUN levels were elevated and relative kidney weight was increased.

Jenkins et al. (1972) maintained Wistar rats on diets containing 0.109% p-aminophenol for 13 days. No significant effects were found on food intake hematologic parameters or histology of spleen, kidney or liver.

Intravenous injection of female rats (n=5) with 0.1, 2.1 or 2.8 mmol/kg of p-aminophenol hydrochloride resulted in a dose-dependent histopathology of the proximal convoluted tubule within 48 hours of dosing (Calder et al., 1971). The animals treated with the highest dose suffered complete necrosis of the proximal convoluted tubule accompanied by anuria. The animals treated with the middle dose had necrosis of the distal third of the proximal convoluted tubules accompanied by polyuria. The animals treated with the lowest dose had sporadic necrosis of isolated cells or groups of cells in the proximal convoluted tubule accompanied by no clinical symptoms. Rats treated with 1.4 mM/kg of m-aminophenol hydrochloride or 2.8 mM/kg of o-aminophenol hydrochloride had no histological alterations in the kidney.

Groups of four Fischer 344 rats and groups of four Sprague-Dawley rats received subcutaneous injections of 0, 50, 100, 200 or 400 mg/kg of p-aminophenol hydrochloride (Newton et al., 1983b,c). Urine was collected for 24 hours after dosing at which time the rats were killed and the kidneys removed for histological evaluation. Blood urea nitrogen levels were significantly higher than controls 24 hours after dosing at the two highest dose levels tested (200 and 400 mg/kg) in the F344 rats, but only at the highest dose level tested (400 mg/kg) in the Sprague-Dawley rats. Renal necrosis was detected in the proximal tubules at the lower doses of p-aminophenol, but occurred in both the proximal and distal tubules at the two highest dose levels (200 and 400 mg/kg) in the F344 rats and only at the highest dose level (400 mg/kg) in the Sprague-Dawley rats. The extent of renal necrosis was dose-dependent in both strains; however, the kidneys of the F344 rats had more extensive necrotic changes at all dose levels than the kidneys of the Sprague-Dawley rats. Furthermore, covalent binding of the p-aminophenol to kidney microsomes in vitro was greater in F344 than in Sprague-Dawley rats. As indicated in Section 4.3., higher levels of acetaminophen were present in the urine of Sprague-Dawley rats than of F344 rats after administration of 200 and 400 mg/kg of p-aminophenol (Newton et al., 1983b,c).

In a study designed to evaluate the correlation between renal histopathology and the amount of lactate dehydrogenase in the urine, the urine from an unspecified number of male and female Sprague-Dawley rats treated with a single subcutaneous injection of 0, 12.5, 25, 50 or 100 mg/kg of p-aminophenol was collected for 24 hours after dosing, and the amount of lactate dehydrogenase was reported (Cottrell et al., 1976). The rats were killed 24 hours after dosing and the kidneys were prepared for histological

evaluation. After a dose of 12.5 mg/kg of p-aminophenol, the amount of lactate dehydrogenase in the urine was comparable to controls; however, after doses of 25, 50 or 100 mg/kg, the amount of lactate dehydrogenase in the urine rose to ~400, 1450 and 6500% of the control levels, respectively. In another experiment, an unspecified number of rats were treated with daily subcutaneous injection of 100 mg/kg of p-aminophenol for 3 days (Cottrell et al., 1976). The urine was collected at 24-hour intervals, and the amount of alkaline phosphatase determined. After 3 days the rats were killed and the renal histology evaluated. Although the level of urinary alkaline phosphatase was ~900% of the control value 24 hours after p-aminophenol treatment began, it returned to a level slightly above (~150%) the control levels within 72 hours. In contrast, the histopathological lesions in the kidneys increased in severity from the first to the third day of treatment with p-aminophenol. Although the severity of the histopathological lesions appeared to correlate with the amount of lactate dehydrogenase in the urine within the first 24 hours after treatment with increasing doses of p-aminophenol, the severity of the histopathological lesions that was due to p-aminophenol treatment increased with time; whereas, the level of alkaline phosphatase activity in the urine returned to control levels within 3 days (Cottrell et al., 1976).

Intravenous injection of 300 mg/kg of p-aminophenol hydrochloride into the tail vein of male Sprague-Dawley rats significantly decreased the level of renal, but not hepatic, microsomal glucose-6-phosphatase within 1 and 4 hours after dosing (Crowe et al., 1977a). In vitro treatment of renal microsomes with p-aminophenol did not alter the level of glucose-6-phosphatase. Crowe et al. (1977a,b) concluded that p-aminophenol damaged kidney endoplasmic reticulum membranes.

The amount of histochemically identified alkaline phosphatase in the renal tubular epithelium increased with the increasing severity of histopathological lesions caused in the kidney within 24 hours of subcutaneous injection of 2.5, 5, 10, 20, 30, 50 or 100 mg/kg of p-aminophenol hydrochloride (Gyrd-Hansen, 1974).

Intravenous injection of (3 mmol/kg) p-aminophenol hydrochloride into the tail vein of male albino Wistar rats resulted in decreased ATP content, inhibited gluconeogenesis and the abolition of sodium transport in the proximal convoluted tubule within 1 hour of p-aminophenol hydrochloride administration (Tange et al., 1977).

In vitro evaluation of human red blood cells indicated that incubation with p-aminophenol increased the level of methemoglobin and decreased the level of glutathione but did not result in the formation of Heinz bodies (Miller and Smith, 1970). The increased methemoglobin production (~50% of total hemoglobin) seen in human erythrocytes treated with p-aminophenol was significantly greater in glucose-6-phophate dehydrogenase deficient red blood cells than in normal human red blood cells (Fraser and Vesell, 1968).

In vitro tests indicated that human fetal hemoglobin, prepared from term umbilical cord blood, formed methemoglobin in response to p-aminophenol treatment much more readily than human adult hemoglobin did (Wind and Stern, 1977).

In an abstract Harrison and Jollow (1981) reported that although o-aminophenol induced methemoglobin formation, neither o- nor p-aminophenol induced hemolysis in rats when injected intraperitoneally at a dose of 100 mg/kg bw.

Intraperitoneal administration of 2.28 mM/kg of m-aminophenol, 2.53 mM/kg of p-aminophenol and 3.42 mmol/kg of o-aminophenol to urethane anesthetized mice resulted in convulsive activity in 50% of the animals (Angel and Rogers, 1972). m-Aminophenol, p-aminophenol and o-aminophenol exhibited 50, 40 and 30%, respectively, of the convulsant potency of phenol (Angel and Rogers, 1972).

Transferase activity naturally develops in fetal rat liver between days 18 and 20 of gestation (Wishart and Dutton, 1976; Wishart et al., 1977a). Wishart and Dutton (1977) reported the dose-dependent induction of the glucuronidation of o-aminophenol in fetal rat liver on day 16 of gestation by the intraperitoneal injection of glucocorticoids (cortisol and dexamethasone) into pregnant rats on day 14 and 15 of gestation. Conversely, hypophysectomy by in utero decapitation was reported to prevent the development of transferase activity in fetal livers between days 18 and 20 of gestation, presumably by interrupting the stimulation of glucocorticoids by fetal hypophyseal corticotropin (Wishart and Dutton, 1977). Because the ability of neonatal rats to conjugate o-aminophenol declined between days 13 and 16 of life before increasing to adult levels, Scragg et al. (1983) suggested that rats 13-16 days of age may be more vulnerable to the toxic effects of o-aminophenol, and probably p-aminophenol as well, than either adult or newborn rats.

Administration of dexamethasone or cortisol, both glucocorticoids, to pregnant rats resulted in a dose-dependent increased level of liver transferase activity in the fetuses, which enabled the process of o-aminophenol glucuronidation to occur before the natural time of transferase development (Wishart and Dutton, 1977).

Monoamine oxidase inhibitors such as iproniazid isocarboxazid, nialamide and phenelzine, inhibited the conjugation of o-aminophenol in rat liver slices and in rabbit liver homogenates (Hargreaves, 1968). In an unsuccessful attempt to define a consistent relationship between the hepatocarcinogenicity of several compounds and their effect on glutathione, spermine and spermidine concentration in the liver, Neish (1967) reported that an intraperitoneal injection of 6.4 mg of p-aminophenol/100 g of body weight in a rat resulted in increased levels of glutathione in the liver.

Glucuronidation of o-aminophenol was reported in vitro by a cell strain (MH_1C_1) derived from a Morris rat hepatoma (No. 7791) and another cell strain (R5) derived from rat thyroid fibroblasts, but not by the Chang liver cell line (Dybing and Rugstad, 1972).

Glucuronidation of p-aminophenol, which proceeded at a rate of 50 nmol/mg protein/hour in cultivated rat hepatoma cells (strain No. 7795, designated MH_1C_1) and at a rate of 500 nmol/mg protein/hour in cell homogenates, was inhibited by p-nitrophenol but not by bilirubin or by p-nitrophenol glucuronide (Rugstad and Dybing, 1974)

Kachole et al. (1978) reported that p-aminophenol binds to human term placental microsomes and that the amount of binding increases until the maximal level is reached during the third pregnancy, after which declining amounts of p-aminophenol bind to term placental microsomes. For the fourth and fifth pregnancies, Bergheim et al. (1973) reported that p-aminophenol binds to human term placental microsomes even though no evidence for placental hydroxylation of p-aminophenol was found.

Prostaglandin synthesis in cultivated cells from a mouse neuroblastoma, a rat astrocytoma and a rat renal medulla cell line was inhibited by o-, m- and p-aminophenol (Von Bruchhausen and Baumann, 1982; Baumann et al.,

1983a). Co-oxygenation of p-aminophenol significantly decreased its inhibition of prostaglandin synthetase activity in preparations of rat renal medulla (Baumann et al., 1983b).

Andersson et al. (1982) reported that p-aminophenol caused DNA breakage in cultivated human fibroblast when incubated with prostaglandin synthetase and arachidonic acid. Furthermore, addition of indomethacin or acetylsalicylic acid (prostaglandin synthetase inhibitors) to the culture medium reduced the amount of DNA strand scission to background levels (Andersson et al., 1982).

The oxidation of p-aminophenol hydrochloride to the p-aminophenoxy free radical was catalyzed by prostaglandin synthetase in the presence of arachidonic acid and by horseradish peroxidase in the presence of hydrogen peroxide (Josephy et al., 1983).

Intraperitoneal administration of 3-acetamidophenol to rats resulted in the formation of 3-aminophenol and its subsequent distribution to the liver, kidney and brain, primarily; however, low but persistent levels of 3-aminophenol were reported in the plasma and skeletal muscles (Quitmann et al., 1984).

Mice (B6C3F1 strain) excreted 9.7% of an orally administered dose of nitrobenzene as urinary p-aminophenol within 72 hours of dosing; no p-aminophenol was found in the urine of Fischer 344 or CD rats after oral administration of nitrobenzene (Rickert et al., 1983).

Radioactive p-aminophenol and o-aminophenol were identified as metabolites after isolated rat livers were perfused with ^{14}C-aniline, ^{14}C-phenylhydroxylamine or ^{14}C-nitrosobenzene (Eyer et al., 1980). The Km was 144 μM for the metabolism of aniline to both p- and o-aminophenol;

the Vmax was 51 nmol/minute/g liver wet weight and 16 nmol/minute/g liver wet weight for the metabolism of aniline to p- and o-aminophenol, respectively.

One of the traditional methods of determining the rate of metabolism of aniline is to measure the amount of p-aminophenol produced (Stevens et al., 1980; Chhabra et al., 1972). Conjugated p-aminophenol accounts for 13% of the aniline introduced into a profusion system of the rat liver (Boobis and Powis, 1975). o-Aminophenol and p-aminophenol constituted ~20% of the urinary metabolites in sheep, pigs and rats that were treated orally with aniline (Kao et al., 1978). Trace amounts of o- and p-aminophenol, as well as acetominophen, were reported in Fischer 344 rats after intravenous administration of radioactive aniline hydrochloride (Irons et al., 1980).

One of the metabolites of acetaminophen, the active ingredient in Tylenol (PDR, 1973), is p-aminophenol, which was present in mouse kidney slices in vitro (Carpenter and Mudge, 1981), in the Fischer 344 rats (Newton et al., 1982, 1983b,c), in the Sprague-Dawley rat (Newton et al., 1983a,b) and in the hamster (Gemborys and Mudge, 1981) following treatment with acetaminophen. Although p-aminophenol was produced by both Fisher 344 and by Sprague-Dawley rats, the acetominophen was nephrotoxic only in the Fischer 344 rats (Newton et al., 1983a,b,c). Furthermore, o- and m-aminophenol were not nephrotoxic in the Fischer 344 rats (Newton et al., 1982).

In an abstract, Ozawa et al. (1956) reported that intravenous injection of <100 mg/kg of m-aminophenol produced no toxic effects in rabbits or mice. In another abstract describing the muscular effect of several anti-oxidants, Laborit et al. (1961) reported that the MED in the rabbit, rat or dog of m-aminophenol administered intraperitoneally or intramuscularly was 75 mg/kg

and the lethal dose was 1000 mg/kg. The same abstract (Laborit et al., 1961) reported a MED of 300 mg/kg and a lethal dose also equivalent to 300 mg/kg for p-aminophenol.

Calder et al. (1975) reported that p-aminophenol interfered with the cellular oxidation-reduction system in the rat, and Crowe et al. (1977a,b) reported that p-aminophenol affected, mitochondrial respiration of rats by decreasing the levels of oxidative phosphorylation and ATPase activity.

Kiese et al. (1975) reported that an intravenous dose of 400 mg/kg of p-aminophenol produced extensive renal tubular necrosis in rats, as well as oxidized 25% of the rat's hemoglobin. Without providing any details, Kiese et al. (1975) indicated that tubular necrosis was observed in rats after treatment with 100 mg/kg of p-aminophenol and that the kidney damage produced at this dose was reversible within 2 weeks.

Application of powdered p-aminophenol into one eye of nine New Zealand rabbits resulted in "slight" conjunctivitis which cleared up within 96 hours regardless of whether the eye was washed 20 seconds or 24 hours after p-aminophenol application (Mallinckrodt, Inc., 1983). The iris and cornea were not affected.

Six of 10 rats exposed to p-aminophenol in the air at a concentration of 5.91 mg/ℓ, flowing at a rate of 3.0 ℓ/minute for 60 minutes had histological evidence of "moderate" pulmonary congestion upon examination 14 days after treatment (Mallinckrodt, Inc., 1983). The inhalation of p-aminophenol did not affect body weight gains or produce any gross signs of adverse effects.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The toxic effects of p-aminophenol were examined in rainbow trout (Salmo gairdneri), bluegill sunfish (Lipomis macrochirus) and larval lampreys (Petromyzon marinus) (Applegate et al., 1957). All species exposed at 5.0 mg/ℓ had a LT_{50} of ~13 hours. Applegate et al. (1957) also exposed larval lampreys to o- and m-aminophenol with no observed effect at 5.0 mg/ℓ for 24 hours.

Using the freshwater crustacean, Daphnia magna, Sollman (1949) reported a 48-hour LC_{50} value of 2.0 mg/ℓ for p-aminophenol.

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic exposure to any isomer of aminophenol on aquatic organisms were not located in the available literature cited in the Appendix.

6.3. PLANT EFFECTS

Pertinent data regarding the toxic effects of aminophenols on aquatic plants were not located in the available literature cited in the Appendix.

6.4. RESIDUE

Pertinent data regarding the residues of aminophenols in the aquatic environment were not located in the available literature cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

The distribution and elimination kinetics of ^{14}C-p-aminophenol in the frog (Rana temporaria) and the crayfish (Astacus leptodactylus) were studied by Nagel and Urich (1981). Compounds were injected into frogs and crayfish at 5 and 3 mg/kg, respectively, and tissue levels were determined at 0.5, 2, 4 and 15 hours in frogs and 4, 15 and 45 hours in crayfish. p-Aminophenol

was rapidly eliminated in frogs with apparent retention only in the gall bladder and gut contents. Elimination of p-aminophenol in the crayfish was somewhat slower, with measurable tissue levels at 45 hours after injection. In frogs, renal elimination was the primary route, while in crayfish, the gills were the major route of excretion.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidlines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits for aminophenols were not located in the available literature cited in the Appendix.

7.2. AQUATIC

Pertinent guidelines and standards regarding the protection of aquatic organisms from the toxic effects of any isomer of aminophenol were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

Ingestion of diets containing 0.09-0.2% o- or p-aminophenol by rats for 270-341 days did not result in increased incidences of tumors (Ekman and Strombeck, 1949a,b; Miller and Miller, 1948). o-Aminophenol was not carcinogenic to the urinary bladder of mice receiving implants of pellets containing o-aminophenol into the bladder (Clayson et al., 1958); however, the induction of bladder tumors in mice treated with various other aromatic amines was attributed to the appearance of o-aminophenol in the bladder following metabolism of the aromatic amines (Boyland, 1960). No studies on the carcinogenicity of m-aminophenol were found.

p-Aminophenol was generally negative for reverse mutations in Salmonella typhimurium with and without metabolic activation, but positive for forward mutations in mouse lymphoma cells (see Table 5-2). p-Aminophenol was positive in mice (Wild et al., 1981) but negative in rats (Hossack and Richardson, 1977) in the micronuclues test; positive for SCE in human lymphocytes (Takehisa and Kanaya, 1982) and Chinese hamster V79 cells (Wild et al., 1981), but not in human fibroblasts (Wilmer et al. 1981); positive for chromosome breaks in mouse bone marrow cells (Mitra and Manna, 1971) and inhibition of DNA synthesis in human lymphoblastoid cells (Hayward et al., 1982), but negative for unscheduled DNA synthesis in rat hepatocytes (Probst et al., 1981). m-Aminophenol was negative for reverse mutation in S. typhimurium, for SCE in Chinese hamster cells, and in the micronucleus test in rats and mice (see Table 5-3).

Equivocal results were obtained for reverse mutations in S. typhimurium when o-aminophenol was tested (see Table 5-4). Positive results were obtained in the micronucleus test in mice (Wild et al., 1981) and for SCE in

human cells (Kirchner and Bayer, 1982; Wilmer et al., 1981) and Chinese hamster V79 cells (Wild et al., 1981), but not Chinese hamster bone marrow cells (Kirchner and Bayer, 1982) o-Aminophenol was negative for recessive lethal mutations in Drosophila melanogaster (NTP, 1983).

In a teratogenicity study, pregnant hamsters were treated with p-aminophenol by gavage, by intraperitoneal injection or by intravenous injection on day 8 of gestation (Rutkowski and Ferm, 1982). Pregnant hamsters were also treated intraperitoneally with o- and m-aminophenol. All doses were ≤250 mg/kg. No fetotoxicity or teratogenic effects were observed following oral doses of p-aminophenol; however, dose-related increases in resorptions and malformations occurred after intraperitoneal or intravenous dosing with p-aminophenol and after intraperitoneal dosing with o-aminophenol. Intraperitoneal administration of m-aminophenol was without effect. No fetotoxic or teratogenic effects were observed in the offspring of female rats that were maintained on diets containing 0.13, 0.25 or 0.98% m-aminophenol for 13 weeks prior to and during gestation (Re et al., 1984).

No studies of chronic administration of the aminophenol and their salts were located in the available literature, and only one subchronic study of m-aminophenol (Re et al., 1984) was found.

In the subchronic toxicity study of Re et al. (1984), the middle dose (0.25% of dietary m-aminophenol) resulted in decreased body weight gain and decreased thyroid weight accompanied by increased height of epithelial cells and reduced follicular size. These effects were magnified at the highest dose tested (0.98% of dietary m-aminophenol), and, in addition, the highest dose tested resulted in hemolytic anemia effects (accumulation of iron pigment in liver, kidney and spleen, reduced red blood cell count and hemoglobin level and increased mean corpuscular volume). At the lowest dose

tested (0.13% dietary m-aminophenol), the absolute and relative weight of the thyroid gland was significantly less than controls, but there were no histological alterations. No other effects were reported at the lowest dose tested. A dietary level (0.13%) at which the only reported effect was a change in thyroid weight constitutes a NOAEL.

The 0.13% (1300 ppm) dietary level of m-aminophenol is equivalent to a dosage of 65 mg/kg/day, assuming that a rat eats a daily amount of food equal to 5% of its body weight. It should be noted that the acute administration of aminophenols to animals has resulted in nephrotoxicity, antioxidant effects, formation of methemoglobin, convulsions and muscular effects at doses generally $\geq$75 mg/kg (see Section 5.6.), but administration was generally by intravenous, subcutaneous, intraperitoneal and intramuscular injection. In the only acute oral study, Newton et al. (1982) found no nephrotoxic effects in rats following single oral doses of p-aminophenol of <100 mg/kg. At $\geq$100 mg/kg, BUN levels were elevated and relative kidney weight was increased. Moreover, given the fetotoxicity and teratogenicity of p-aminophenol in hamsters following intraperitoneal and intravenous dosing compared with the lack of such effects following oral administration at the same doses (Rutkowski and Ferm, 1982) aminophenols appear to be less toxic when administered orally. Therefore, it may be appropriate to derive an ADI for m-aminophenol based on the study of Re et al. (1984).

Using the NOAEL for oral exposure of 65 mg/kg/day and an uncertainty factor of 1000 (10 to approximate chronic exposure, 10 for interspecies extrapolation and 10 to protect the most sensitive individuals of the human population), an ADI for m-aminophenol of 0.065 mg/kg/day or 4.55 mg/day for a 70 kg man is obtained.

Because chronic and subchronic studies of o-aminophenol and p-aminophenol and their salts were not available, no individual values for ADIs for these compounds can be derived. It is difficult to compare the relative oral toxicity of the three isomers and their salts based on the available data. In the teratology study by Rutkowski and Ferm (1982), however, both o- and p-aminophenol administration to hamsters by the intraperitoneal route resulted in dose-related fetotoxic and teratogenic effects, while m-aminophenol at the same intraperitoneal doses was without effect. Therefore, the ADI for m-aminophenol may not be sufficiently protective against the toxic effects of its isomers.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY RANKING (RQ) BASED ON CHRONIC TOXICITY

Only two studies were available that examined the teratogenicity or effects of long-term oral administration of aminophenols (see Sections 5.3. and 5.5.). No fetotoxic or teratogenic effects were observed in the offspring of hamsters treated orally with ≤200 mg/kg p-aminophenol on day 8 of gestation (Rutkowski and Ferm, 1982). Re et al. (1984) maintained 35 female rats on diets containing m-aminophenol at 0, 0.13, 0.25 and 0.98% for 13 weeks, at which time 10 rats/group were killed and necropsied. The remaining 25 rats/group were mated with untreated males and continued on their respective diets until day 20 of gestation. The high-dose level pregnant rats gained significantly less weight than the controls, but no other signs of maternal toxicity were observed during gestation. No significant increased incidences of number of implantation sites, resorptions, malformations or fetal deaths were observed.

In the 13-week part of the study of Re et al. (1984), dietary exposure of rats at 0.98% m-aminophenol resulted in the development of hemolytic anemia, as evidenced by decreased hemoglobin levels and red blood cell counts, increased mean corpuscular volume and accumulation of iron-positive pigment in livers, spleens and kidneys. Decreased body weight gain was observed at 0.25 and 0.98%. At 0.98%, the relative thyroid weight was significantly increased, but at 0.13 and 0.25%, the relative thyroid weight was significantly decreased. Histologic changes in the thyroid were observed at 0.25 and 0.98% and consisted of decreased follicular size and increased height of epithelial cells.

The data used to calculate the CSs for these effects are presented in Table 9-1. The dietary exposures 0.13, 0.25 and 0.98% (1300,2500 and 9800 ppm) were transformed to dosages of 65, 125 and 490 mg/kg/day, respectively, assuming that a rat consumes a daily amount of food equal to 5% of its body weight. The transformed doses were multiplied by the cube root of the ratio of the rat weight (assumed to be 0.35 kg) to the human weight (assumed to be 70 kg) and by the human body weight and by dividing by an uncertainly factor of 10 to approximate a human chronic MED.

At 490 mg/kg/day, the human MED is 586.5 mg/day, corresponding to an RV_d of 1.3. The effect of hemolytic anemia warrants an RV_e of 7. The product of the RV_d and RV_e is the CS of 9.1, corresponding to an RQ of 1000. The lowest dose at which histologic changes in the thyroid and decreased body weight occurred was 125 mg/kg/day corresponding to an MED of 149.6 mg/day and an RV_d of 2.2. The effects are given an RV_e of 4, the CS is 8.8 and the RQ is 1000. At 65 mg/kg/day, the MED is 77.8, corresponding to an RV_d of 2.7. Although the significance of decreased thyroid weight is uncertain, organ weight changes warrant an RV_e of 4; the CS is 10.8 and the RQ is 1000.

The data resulting in the highest CS, that is, decreased thyroid weight at 65 mg/kg/day, is recommended as the basis of the RQ for m-aminophenol (Table 9-2).

No long-term studies of o- or p-aminophenol or their salts were available, precluding the derivation of RQ values (Tables 9-3 and 9-4). As discussed in Chapter 8, it is not appropriate to recommend an RQ for these compounds based on analogy to m-aminophenol.

TABLE 9-1

Composite Scores for Oral Exposure to m-Aminophenol in the Rat[a]

Dose (mg/kg/day)	Chronic Human MED (mg/day)[b]	RV_d	Effect	RV_e	CS	RQ
490 for 13 weeks	586.5	1.3	Hemolytic anemia evidenced by iron pigment accumulation in kidney, spleen and liver; decreased hemoglobin levels and red blood cell counts and increased mean corpuscular volume; increased thyroid weight	7	9.1	1000
125 for 13 weeks	149.6	2.2	Decreased body weight, decreased thyroid weight accompanied by epithelial hyperplasia	4	8.8	1000
65 for 13 weeks	77.8	2.7	Decreased thyroid weight	4	10.8	1000

[a]Source: Re et al., 1984

[b]The animal doses were divided by an uncertainty factor of 10 to approximate chronic exposure.

TABLE 9-2

m-Aminophenol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	77.8 mg/day
Effect:	decreased thyroid weight
Reference:	Re et al., 1984
RV_d:	2.7
RV_e:	4
Composite Score:	10.8
RQ:	1000

*Equivalent human dose

TABLE 9-3

o-Aminophenol, o-Aminophenol Sulfate, o-Aminophenol Hydrochloride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose*:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ

*Equivalent human dose

TABLE 9-4

p-Aminophenol, p-Aminophenol Sulfate, p-Aminophenol Hydrochloride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:

Dose*:

Effect:

Reference:

RV_d:

RV_e:

Composite Score:

RQ: Data are not sufficient for deriving an RQ

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*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Dietary exposure of rats to o- or p-aminophenol at 0.09-0.2% did not result in increased incidences of tumors (Ekman and Strombeck 1949a,b; Miller and Miller, 1948). Clayson et al. (1958) implanted pellets containing o-aminophenol into the bladders of mice, but did not observe a carcinogenic response (see Table 5-1). Boyland (1960) attributed the induction of bladder tumors in mice by various aromatic amines to the appearance of o-aminophenol in the bladder following metabolism of the aromatic amines. No other information on the carcinogenity of these compounds was available.

Because of insufficient data, p-aminophenol, p-aminophenol hydrochloride, p-aminophenol sulfate, m-aminophenol, o-aminophenol, o-aminophenol hydrochloride and o-aminophenol sulfate would all be classified as EPA Group E. This group includes those chemicals for which no significant carcinogenic activity was observed in animals nor which any supportive positive epidemiological data exists.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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